(19) Europäische Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 839 458 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.05.1998 Bulletin 1998/19

(51) Int Cl.[6]: **A23L 1/30**, A23L 1/035, A61K 31/56

(21) Application number: **97308894.1**

(22) Date of filing: **05.11.1997**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **05.11.1996 JP 308748/96**

(71) Applicant: **RIKEN VITAMIN CO., LTD.**
Chiyoda-ku, Tokyo (JP)

(72) Inventors:
- **Nakano, Takahisa**
  Chiba-City, Chiba-Prefecture (JP)
- **Kikuchi, Hidekazu**
  Chiba-City, Chiba-Prefecture (JP)
- **Itoh, Shinpei**
  Yachiyo-City, Chiba-Prefecture (JP)

(74) Representative: **Stuart, Ian Alexander et al**
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

(54) Phytosterol compositions and their production

(57) The present invention discloses oil solubilized solutions and foods containing phystosterols containing sitosterols with improved stability, for better absorption of those phytosterols into the body through their oil solubilization, as well as a process for their production; the oil solubilized solutions and foods of the invention are characterized by addition of vitamin E and emulsifiers to sitosterol-containing plant sterols to render the plant sterols soluble in oil, and particularly by extraction of the sitosterol from natural plant components, either alone or as a composition containing other phytosterol components, and by inclusion of vitamin E, emulsifiers which are liquid at room temperature, and glycerin esters of medium chain fatty acids of 6-12 carbon atoms; the process for producing oil solubilized plant sterols according to the invention is characterized by adding vitamin E and emulsifiers to phystosterols containing sitosterols to render the plant sterols soluble in oil.

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Description

The present invention relates to phytosterol compositions and to a process for their production. It particularly relates to oil solubilized solutions and foods, hyperplasia and prophylactic effects against various diseases such as as hyperlipidemia and the like, as well as to a process for their production. and the like, as well as to a process for their production.

Phytosterols such as sitosterols have long been known for their inhibiting effects on cholesterol absorption, and have been used as clinical or non-prescription drugs for improvement in hyperlipidemia. However, because phytosterols tend to be poorly soluble in oil as well as water, they have been prepared either as oil suspensions or in the form of powder or granules.

Water solubilization of phytosterols is disclosed in Japanese Laid-open Patent Publication No.Sho-50-89520 and 53- 31210, but these relate to processes for producing sterol injections, not for oral administration.

It is also known that combination of phytosterols and ethylene oxide improve the solubility in water and organic solvent due to the length of the ethylene oxide chain, but this is applied for toiletries, and not for foods.

Insoluble form of phytosterols are not only poorly absorbed, but also inconvenient for common use as food additives, therefore improvements have been desired in these areas. In Germany, sitosterols have been used for symptom improvement of benign prostatic hyperplasia (see R.R. Berges, J. Windeler, H. J. Trampish, Th Senge and the β - sitosterol study group. Randomized, placebo-controlled, double-blind clinical trial of β-sitosterol in patients with benign prostatic hyperplasia. The Lancet, 345, 1529, 1995), but it is used in powder form because of its insoluble nature.

Refer to the following documents for uses of phytosterols as cholesterol-lowering agents.

A. Lees A.M., Mok H.Y.I., Lees R.S., McCluskey M.A. and Grundy S.M., Phytosterols as Cholesterol-Lowering Agents: Clinical Trials in Patients with Hypercholesterolemia and Studies or Sterol Balance., Atherosclerosis, 28, 325, 1997.

B. MATSUMOTO Shinzo. et al., Double-Blind Clinical Trials for ST-2, Shinyaku to Rinsho, 10, 2527 (1973).

C. SANO Tadahiro., Antiplatelet Effect of Unsaponifiable Soybean ST-2 (3rd Report), Rinsho to Riken, 59, 2611 (1982)

D. KAJIYAMA Goro. et al., Effect of DS-4046 on Hyperlipidemia, Yakuri to Chiryo, 16, 2965 (1988)

E. OTANI Reiji., Clinical Use Results for Sometol Against Hyperlipidemia, Yakuri to Chiryo, 12, 4155 (1984)

F. TAKEI Yoshio., Clinical Use Results for Sometol, Kiso to Rinsho, 19, 1684 (1985)

G. HATA Yoshichika. et al., Effects of Unsaponifiable Soybean (Soysterol) on Hyperlipidemia, Geriat. Med., 24, 1635 (1986)

Preferred embodiments of the present invention may provide oil solubilized solutions and foods containing phytosterols such as sitosterol, and particularly may provide oil solubilized solutions and foods containing plant sterols such as sitosterol with improved stability, for better absorption of the phytosterols into the body through their oil solubilization, as well as a process for their production.

The present invention provides a food including a phytosterol containing sitosterol, characterized by addition of vitamin E and an emulsifier to the phytosterol containing sitosterol for solubilization of the phytosterols in oil.

Preferably said sitosterol is extracted from natural plant components, either alone or as a composition containing other phytosterol components.

Preferably the food contains a oil-solubilized phytosterol solution containing vitamin E in an amount of at least 5 wt%.

Preferably the emulsifier is a liquid emulsifier at room temperature, and is present in an oil-solubilized phytosterol solution in an amount of at least 5 wt%; preferably the food contains 0-10 wt% of a glycerin ester of a medium chain fatty acid of 6-12 carbon atoms.

In another aspect the invention provides an oil-solubilized solution containing 1-50 wt% of a phytosterols containing sitosterol which is soluble in oil. The solution preferably contains vitamin E and an emulsifier for solubilization of the phytosterols in oil.

Preferably said sitosterol is extracted from natural plant components either alone or as a composition containing other phytosterol components.

Preferably the oil-solubilized phytosterol solution contains vitamin E in an amount of at least 5 wt%.

Preferably the solution contains an emulsifier which is liquid at room temperature, and is present in the oil-solubilized phytosterol solution in an amount of at least 5 wt%;

Preferably the oil-solubilized solution contains both vitamin E and an emulsifier which is liquid at room temperature and the emulsifier contains at least 60 wt% of oleic acid or lauric acid either alone or in combination;

Preferably the oil-solubilized solution contains 0-10 wt% of a glycerin ester of a medium chain fatty acid of 6-12 carbon atoms.

In a third aspect the invention provides a process for producing an oil-solubilized plant sterol composition charac-

terized by adding vitamin E and an emulsifier to a phytosterol comprising sitosterol for solubilization of the phytosterol in oil.

The present inventors have achieved oil solubilization of sitosterol and other phytosterols for stabilization of sitosterol to provide compositions which are readily absorbed in the human body, and have thus facilitated the processing of various types of foods. In particular, the pr sent inventors have conducted diligent research on oil solubilization of sitosterol, and as a result have found that an oil-solubilized solution containing vitamin E and an emulsifier which is liquid at room temperature, allows preparation of stable and highly absorbable phytosterols , which has been difficult according to the prior art.

It has also been found that the addition of MCTs (glycerin esters of medium chain fatty acids of 6-12 carbon atoms, especially triglycerides) improves the fluidity of the compositions, while also providing a better feel to the tongue and being easy to use in foods.

Some embodiments of the present invention will now be explained in further detail with reference to the accompanying drawings in which

Fig 1 is a bar chart showing the effects of a composition embodying the invention on various parameters; and
Fig 2 is a bar chart showing the aggregate effect..

The sitosterol may be a phytosterol which is obtained by separation from distillate and the like generated by deodorizing processes at plant oil production factories. Sitosterol is a type of phytosterol which is a constituent of the cell membrane of plants, together with campesterol and stigmasterol, and sitosterol is the most abundant sterol in the plant.

Sterols are classified into animal, plant, microbial and marine sterols, but according to the present invention phytosterol comprising sitosterol are effective. Known phytosterols other than those containing sitosterol include stigmasterol, campesterol and brassicasterol. Sitosterol is the most abundant sterol in the plant, and is widely found in plant seed oils and other plant parts. Stigmasterol is abundant in soybean, coconuts and cottonseed, campesterol is abundant in soybean, rapeseed and wheat, and brassicasterol is abundant in rapeseed. The sitosterol used for the invention need not be separated as a single product, and may be used in admixture with the other aforementioned sterols, etc.

The vitamin E to be used according to the present invention may be in the form of α-, β-, γ, or δ-tocopherol, and of course there is no difference in solubility even with mixtures thereof. Consequently, there is no difference in the solubility regardless of the extraction source of the vitamin E.

The emulsifier to be used according to preferred embodiments is a liquid emulsifier at room temperature, examples of which include glycerin fatty acid esters, diglycerin fatty acid esters, polyglycerin fatty acid esters, organic acid glycerin fatty acid esters, propylene glycol fatty acid esters, sorbitan fatty acid esters and sucrose fatty acid esters, which may be used either alone or in combinations.

In addition, the emulsifier does not necessarily need to be highly purified by distillation or the like, and it may be a reaction mixture.

In particular, emulsifiers containing high concentrations of oleic acid are preferable, among which oleic acid monoglyceride, oleic acid diglyceride and oleic acid propylene glycol have high solubility and improve fluidity. The emulsifier used according to the present invention may improve the uncomfortable waxy feeling on the tongue which is characteristic of phytosterols. Therefore the compositon of the present invention can be easily used in a wide variety of foods.

MCTs are glycerin esters of middle chain fatty acids of 6-12 carbon atoms, and are widely abundant in coconut oil. Among oils, phytosterols dissolve most easily in MCTs, which dissolve phytosterols up to a concentration of about 5 wt%, and MCTs with a tricaprilin (C10) composition are most suitable as they dissolve phytosterols even up to a concentration of 7 wt%. Plant sterols will dissolve in MCTs alone up to a concentration of about 7 wt%, but the solubility is drastically improved by combination of vitamin E and an emulsifier as according to the invention. Here, the MCT can be used in a range of 0-10 wt%, but preferably 0-5 wt%. The use of MCTs according to the invention is effective both for improving the fluidity of the oil solubilized solution and for providing a much better feel to the tongue when used with the emulsifier. MCTs also help in reducing the amount of vitamin E required, and therefore the use of MCTs has high industrial significance.

Generally, the oil solubilized phytosterol comprising sitosterol is present in the oil- solubilized solution in an amount of 1-40 wt%, and oil- solubilized solutions containing it in amount of 15-30 wt% are easiest to use from an industrial standpoint.

Because of the low solubility of phytosterols as described above, they are almost always employed in powder or suspension form even when used as cholesterol-lowering agents or benign prostatic hyperplasia improving agents. Considering that solubility of sterols into bile acid micelles is an essential for absorption, the oil- solubilized phytosterols of the present invention are expected to be better absorbed and provide better pharmacological effects than powders or suspensions.

There are no restrictions to the foods and drinks which may contain these oil-solubilized phytosterolss, and they

may include soft capsules, microcapsules, cooking oils, shortening, dressings, margarine, butter, mayonnaise, cookies, etc.

The present invention also encompasses addition of fat crystal modifiers such as lecithin, and other additives.

Embodiments of food production according to the present invention will now be provided.

Embodiment 1

Soft capsules (gelatin-glycerin capsule) were prepared from an oil-solubilized preparation having the following composition,

Plant sterol (Rikesterol, Riken Vitamin Co.)	20 wt%
Vitamin E (SDC-RD-50, Riken Vitamin Co.)	50 wt%
Propylene glycol monooleate (Rikemal P0-100, Riken Vitamin Co.)	30 wt%

Embodiment 2

The following oil-solubilized preparation was made with the following composition.

Plant sterol (Rikesterol, Riken Vitamin Co.)	20 wt%
Vitamin E (SDC-RD-50, Riken Vitamin Co.)	45 wt%
Reactive mixture of glycerol oleate (POEM 0L-200, Riken Vitamin Co.)	16 wt%
Propylene glycol monooleate (Rikemal PO-100, Riken Vitamin Co.)	15 wt%
MCT (Actor M-2, Riken Vitamin Co.)	5 wt%

The oil-solubilized preparation was then used to make a dressing having the following composition.

Oil-solubilized preparation	90 g
Salad oil	570 g
Vinegar	250 g
Mustard	1 g
Pepper	1 g
Lemon juice	45 g
Onion juice	35 g
Sodium glutamate	3 g
Salt	5 g

Embodiment 3

The oil-solubilized preparation from Embodiment 2 was used to make mayonnaise having the following composition.

Oil-solubilized preparation	90 g
Salad oil	646 g
Vinegar	120 g
Egg yolk	100 g
Dispersed mustard	20 g
Sodium glutamate	2 g
Salt	22 g

Embodiment 4

The oil-solubilized preparation from Embodiment 2 was used to make margarine having the following composition.

Oil-solubilized preparation	300 g
Oil (liquid oil + hardened oil)	520 g
Water	148.5 g
Skim milk powder	15 g
Salt	14 g
Lecithin	1 g
Flavoring	0.49 g
β-carotene	0.01 g

Embodiment 5

The margarine prepared in Embodiment 4 was used to make cookies having the following composition.

Margarine of Embodiment 4	200 g
Butter	100 g
Sugar	180 g
Egg white	55 g
Flour	461 g
Baking soda	1 g
Salt	3 g

Effective examples of the present invention will now be provided.

Fourteen males (38-74 years of age, average 59) with a tendency to dysuria due to benign prostatic hyperplasia were asked to take soft capsules of the oil-solubilized preparation of Embodiment 1 containing 30 mg of sitosterol, at a frequency of 2 capsules 3 times a day after each meal, for a period of 3 months, and the changes in urination before and after the period were noted by autodiagnosis according to the international prostate symptom score (IPSS) shown in Table 1. The results are shown in Table 2 and Figs 1 and 2.

The effectiveness of the present invention was confirmed by the improved effect on dysuria due to benign prostatic hyperplasia, as shown in Table: 2 and Figs 1 and 2.

The cookies of Example 5 also exhibited the same effect.

According to the present invention, there are provided compositions wherein sitosterol and other phytosterols are stabilized by their oil solubilization for improved absorption in the human body, as well as oil solubilized solutions and foods which can be easily processed and which have an improving effect on benign prostatic hyperplasia, and a process for their production.

Table 1

INTERNATIONAL PROSTATE SYMPTOM SCORE (I - PSS)						
	A	B	C	D	E	F
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating ?	0	1	2	3	4	5

Note:
A - - None
B - - Less than 1 of 5 times
C - - Less than 1 of two times
D - - About 1 of 2 times
E - - At least 1 of 2 times
F - - Almost always

Table 1 (continued)

INTERNATIONAL PROSTATE SYMPTOM SCORE (I - PSS)						
	A	B	C	D	E	F
2. Over the past month, how often have you had to urinate again less than two hours aftr you finished urinating	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urination ?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination ?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream ?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination ?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 or more times
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning ?	0	1	2	3	4	5
Total I - PSS Score S =						

Note:
A - - None
B - - Less than 1 of 5 times
C - - Less than 1 of two times
D - - About 1 of 2 times
E - - At least 1 of 2 times
F - - Almost always

Table 2

	Before test	After 1 month	After 2 months	After 3 months
Residual urine feeling	1.93	1.57	1.5	1.36
Urination frequency	2.57	2.07	1.93	1.5
Halted urine	1	1.36	0.79	0.5
Postpone urine	2	1.21	1.43	0.86
Urinary stream	4	2.93	2.21	2.21
Straining	1.71	1.29	1.07	0.86
Nocturia	1.64	1.29	1.43	1.14
	Before test	After 1 month	After 2 months	After 3 months
IPSS	14.86	11.71	10.36	8.43

Claims

1. A food including a phytosterol comprising sitosterol characterised by the addition of vitamin E and an emulsifier to the phytosterol comprising sitosterol for solubilization of the phytosterol in oil.

2. A food according to claim 1 wherein said sitosterol was extracted from natural plant components, either alone or as a composition containing other phytosterol components.

3. A food according to claim 1 or 2 which contains and/or was formed from an oil-solubilized phytosterol solution containing vitamin E in an amount of at least 5 wt%.

4. A food according to any of claims 1 to 3 which contains and/or was formed from an oil-solubilized phytosterol solution in which the emulsifier was present in an amount of at least 5 wt%; and said emulsifier is a liquid emulsifier at room temperature.

5. A food according to any of claims 1 to 4 which contains and/or was formed from an oil-solubilized phytosterol solution containing 0-10 wt% of a glycerine ester of a medium chain fatty acid of 6-12 carbon atoms.

6. An oil-solubilized solution containing 1-50 wt% of a phytosterol comprising sitosterol which is soluble in oil.

7. An oil-solubilized solution according to claim 6 wherein vitamin E and an emulsifier were added to the phytosterol for solubilization of the phytosterol in oil.

8. An oil-solubilized solution according to claim 7 wherein the emulsifier contains at least 60 wt% of oleic acid or lauric acid either alone or in combination.

9. An oil-solubilized solution according to claim 6, 7 or 8 wherein a said sitosterol was extracted from natural plant components, either alone or as a composition containing other phytosterol components.

10. An oil-solubilized solution according to claim 6, 7, 8 or 9 which contains vitamin E in an amount of at least 5 wt%.

11. An oil-solubilized solution according to any of claims 6 to 10 which contains an emulsifier which is liquid at room temperature and is present in the oil-solubilized phytosterol solution in an amount at least 5 wt%.

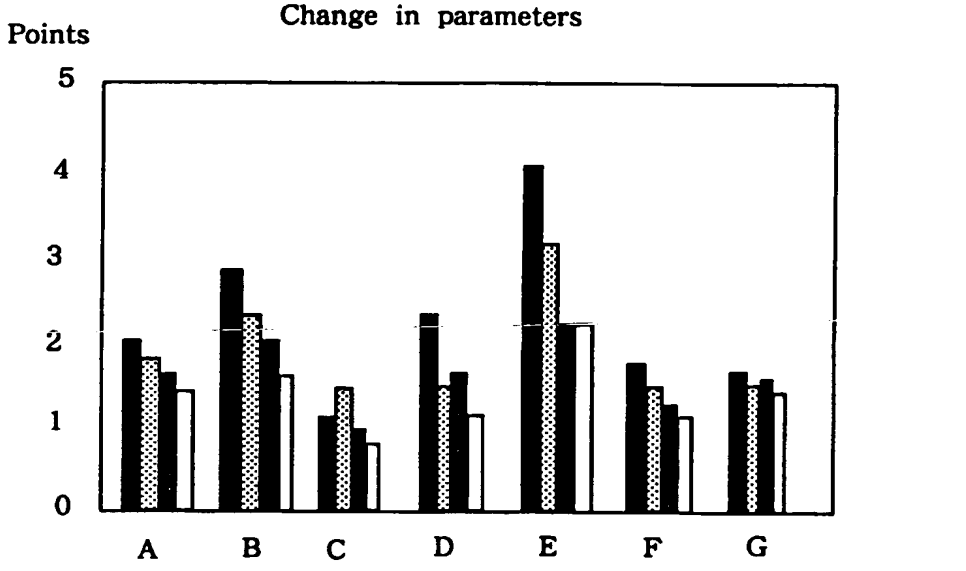
12. An oil-solubilized solution according to any of claims 6 to 11 containing 0-10 wt% of a glycerine ester of a medium chain fatty acid of 6-12 carbon atoms.

13. A process for producing an oil-solubilized plant sterol, characterised by adding vitamin E and an emulsifier to a phytosterol comprising sitosterol for solubilization of the phytosterol in oil.

14. A pharmaceutical composition comprising an oil-solubilized solution according to any of claims 6-12.

15. Use of an oil-solubilized composition according to any of claims 6-12 in the manufacture of a composition for the treatment or prophylaxis of benign prostatic hyperplasia or hyperlipidemia.

Fig 1



Note : Parameters

A – – – Residual urine feeling

B – – – Urination frequency

C – – – Halted urine

D – – – Urine control

E – – – Uirne volume

F – – – Straining

G – – – Nocturnal urination

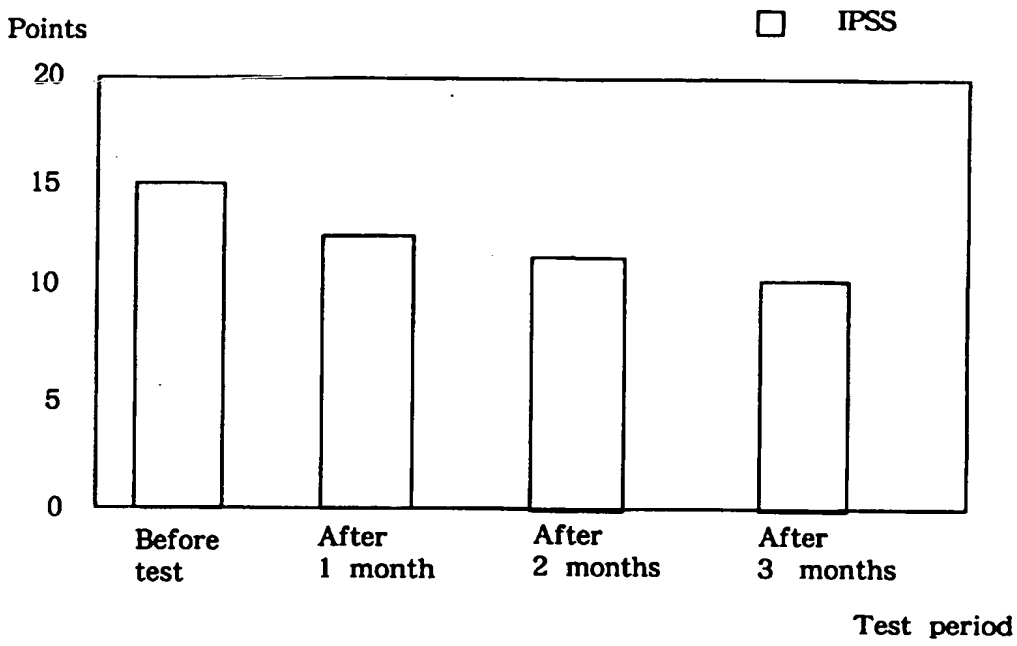
Before test

After 1 month

After 2 months

After 3 months

Fig 2


Points
IPSS
20
15
10
5
0
Before test
After 1 month
After 2 months
After 3 months
Test period

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 8894

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 092 076 A (NESTLE SA) * page 3, line 24 - line 28; examples 3,4 * ---	1-15	A23L1/30 A23L1/035 A61K31/56
X	GB 931 115 A (LABORATORIES ROBAPHARM) * page 2, line 49 - line 55 * ---	1-15	
X	US 5 523 087 A (SHLYANKEVICH MARK) * examples 1,2 * ---	1-15	
X Y	US 5 244 887 A (STRAUB CARL D) * column 6, line 3 - line 29 * ---	1-15 1-15	
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 379 (C-463), 10 December 1987 & JP 62 148424 A (RIKEN VITAMIN CO LTD), 2 July 1987, * abstract * ---	1-15	
X	GB 1 298 047 A (ROELOF WILKE LIEBENBERG) * page 1, left-hand column, line 33 - line 34 * ---	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A23L A61K
P,X	WO 96 38047 A (UNILEVER NV ;UNILEVER PLC (GB); LIEVENSE LOURUS CORNELIS (NL)) * page 13, line 13 - line 20 * ---	1-15	
Y	US 3 085 939 A (MILTRON WRUBLE ET AL.) * column 1, line 55 - line 64 * -----	1-15	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	22 January 1998	Bendl, E

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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